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PATENT COOPERATION TREATY

DOCKETED sf.

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
HAMILTON, BROOK, SMITH
& REYNOLDS, P.C.
Attn. Sanders, Deirdre E.
530 Virginia Road
P.O. Box 9133
Concord, MA 01742-9133
UNITED STATES OF AMERICA

Date of mailing *(day/month/year)*	07/06/2005
Applicant's or agent's file reference: 3518.1015002	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US2004/024725	International filing date *(day/month/year)* 30/07/2004
Applicant: DEPUY SPINE, INC.	

FOREIGN DOCKETING
SRU-07JUL2005 WDF-07SEP2005
WDD-07AUG2005
WDM-02SEP2005
Completed By: SDL

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sylvia Hermier

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JUN 13 2005
HAMILTON, BROOK,

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
3518.1015002		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/024725	30/07/2004	30/07/2003
Applicant		
DEPUY SPINE, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 12 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☒ **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established by this Authority to read as follows:

TREATMENT OF INFLAMED JOINTS

5. With regard to the **abstract,**
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2004/024725

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to trans-capsularly administering into a diseased joint a high specificity antagonist selected from the group consisting of: i) an inhibitor of a pro-inflammatory interleukin; ii) an inhibitor of TNF-alpha synthesis; iii) an inhibitor of membrane-bound TNF-alpha; iv) an inhibitor of a natural receptor of TNF-alpha; v) an inhibitor of NO synthase, vi) an inhibitor of PLA2 enzyme; vii) an anti-proliferative agent; viii) an anti-oxidant; ix) an apoptosis inhibitor selected from the group consisting of EPO mimetic peptides, EPO mimetibodies, IGF-I, IFG-II, and caspase inhibitors, and x) an inhibitor of MMPs; and xi) an inhibitor of p38 kinase.
Compounds include Rapamycin, NG-Monomethyl-L-Arginine, Infliximab, L-NIL, IGF-1, IGF-2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/024725

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-83 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4,30,34-66,80-82 (partially) 5-11,67-75

   Use of an inhibitor of a pro-inflammatory interleukin for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

2. claims: 1-4,30,34-66,80-82 (partially) 12-15,76-79,83

   Use of an inhibitor of TNF-alpha synthesis, an inhibitor of membrane-bound TNF-alpha or an inhibitor of a natural receptor of TNF-alpha for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

3. claims: 1-4,30,34-65,80-82 (partially) 19-21

   Use of an inhibitor of NO synthase for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

4. claims: 1-4,30,34-65,80-82 (partially) 22

   Use of an inhibitor of PLA2 enzyme for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

5. claims: 1-4,30,34-65,80-82 (partially) 23-27

   Use of an inhibitor of an anti-proliferative agent for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

6. claims: 1-4,30,34-65,80-82 (partially) 28

   Use of an anti-oxidant for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

7. claims: 1-4,30,34-65,80-82 (partially) 31-33

   Use of an apoptosis inhibitor for the manufacture of a medicament for treating an inflamed orthopedic joint.

   ---

8. claims: 1-4,30,34-65,80-82 (partially) 29

   Use of an inhibitor of MMP for the manufacture of a medicament for treating an inflamed orthopedic joint.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a diaryl imidazole for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

10. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a diaryl N,N' diaryl urea or a N,N-diarylurea for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

11. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a benzophenone for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

12. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a pyrazole ketone for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

13. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a indole amide for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

14. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a diamide for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

15. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a quinazoline for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

16. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a pyrimido[4,5-d]pyrimidinone for the manufacture of a medicament for treating an inflamed orthopedic joint.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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17. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a pyridylamino-quinazoline for the manufacture of a medicament for treating an inflamed orthopedic joint.

---

18. claims: 1-4,30,34-65,80-82 (partially) 18

Use of an inhibitor of a 1-aryl-2-pyridinyl heterocycle as specified in claim 18 for the manufacture of a medicament for treating an inflamed orthopedic joint.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/024725

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/436 A61K38/30 A61K31/198 A61K39/395 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/28828 A (AMGEN BOULDER INC; COLLINS, DAVID, S; BEVILACQUA, MICHAEL, P) 14 August 1997 (1997-08-14) abstract page 5, line 23 - page 9, line 5 page 10, line 7 - page 11, line 29 page 55, line 3 - page 60, line 20 page 64, lines 4-19 page 75, lines 8-32; claims 1-37; examples 2-4 ----- -/--	1-11,30, 34-75, 80-82

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2005	07 06 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/24477 A (AMGEN INC; BENDELE, ALISON, M; SENNELLO, REGINA, M) 11 June 1998 (1998-06-11) abstract; claims 1-6 page 1, lines 5-9 page 5, lines 5-13 page 6, line 23 - page 8, line 32 page 43, line 29 - page 45, line 22	1-11,30, 34-75, 80-82
X	US 6 294 170 B1 (BOONE THOMAS C ET AL) 25 September 2001 (2001-09-25) abstract column 5, line 46 - column 6, line 14 column 27, line 4 - column 33, line 12	1-11,30, 34-75, 80-82
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X	GABAY C: "IL-1 TRAP" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 4, no. 5, May 2003 (2003-05), pages 593-597, XP009017868 ISSN: 0967-8298 the whole document	1-11,30, 34-75, 80-82
X	DAYER J-M: "THE PIVOTAL ROLE OF INTERLEUKIN-1 IN THE CLINICAL MANIFESTATIONS OF RHEUMATOID ARTHRITIS" RHEUMATOLOGY, OXFORD UNIVERSITY PRESS, LONDON, GB, vol. 42, no. SUPPL 2, May 2003 (2003-05), pages II03-II10, XP008041555 ISSN: 1462-0324 the whole document	1-11,30, 34-75, 80-82
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-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/85179 A (CLEMSON UNIVERSITY) 15 November 2001 (2001-11-15) the whole document -----	1
X	EP 0 438 234 A (KITA, KIYOSHI) 24 July 1991 (1991-07-24) the whole document -----	1
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/024725

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INTERI IONAL SEARCH REPORT

Information on patent family members

Inter. ..nal Application No
PCT/US2004/024725

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/024725	30.07.2004	30.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/436, A61K38/30, A61K31/198, A61K39/395, A61P19/02

Applicant
DEPUY SPINE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-11,30,34-75,80-82 (partially) 12-29,31-33,76-79,83

because:

☒ the said international application, or the said claims Nos. 1-11,30,34-75,80-82 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-11,30,34-75,80-82 (partially) 12-29,31-33,76-79,83

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4,30,34-66,80-82 (partially) 5-11,67-75

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-11,30,34-75,80-82
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-11,30,34-75,80-82
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

Claims 1-11,30,34-75,80-82 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Present claim 1-11,30,34-75,80-82 relate to a method defined by reference to the following parameters:
an inhibitor of a pro-inflammatory interleukin, an inhibitor of a pro-inflammatory interleukin wherein the interleukin is IL-1, IL-1beta, IL-2, IL-6, IL-8, IL-12, IL-19.
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the use of the inhibitors specifically mentioned in the description on page 19, lines 20-24, i.e. Kineret, IL1-Receptor Type 2 and IL-1 Trap.

No Written Opinion will be formulated with respect to subject matter which is not covered by the search report.

Re Item IV.

The separate inventions/groups of inventions are:

1. Claims 1-4,30,34-66,80-82 (partially) 5-11,67-75
   Use of an inhibitor of a pro-inflammatory interleukin for the manufacture of a medicament for treating an inflamed orthopedic joint.

2. Claims 1-4,30,34-66,80-82 (partially) 12-15,76-79,83
   Use of an inhibitor of TNF-alpha synthesis, an inhibitor of membrane-bound TNF-alpha or an inhibitor of a natural receptor of TNF-alpha for the manufacture of a medicament for treating an inflamed orthopedic joint.

3. Claims 1-4,30,34-65,80-82 (partially) 19-21
Use of an inhibitor of NO synthase for the manufacture of a medicament for treating an inflamed orthopedic joint.

4. Claims 1-4,30,34-65,80-82 (partially) 22
Use of an inhibitor of PLA2 enzyme for the manufacture of a medicament for treating an inflamed orthopedic joint.

5. Claims 1-4,30,34-65,80-82 (partially) 23-27
Use of an inhibitor of an anti-proliferative agent for the manufacture of a medicament for treating an inflamed orthopedic joint.

6. Claims 1-4,30,34-65,80-82 (partially) 28
Use of an anti-oxidant for the manufacture of a medicament for treating an inflamed orthopedic joint.

7. Claims 1-4,30,34-65,80-82 (partially) 31-33
Use of an apoptosis inhibitor for the manufacture of a medicament for treating an inflamed orthopedic joint.

8. Claims 1-4,30,34-65,80-82 (partially) 29
Use of an inhibitor of MMP for the manufacture of a medicament for treating an inflamed orthopedic joint.

9. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a diaryl imidazole for the manufacture of a medicament for treating an inflamed orthopedic joint.

10. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a diaryl N,N' diaryl urea or a N,N-diarylurea for the manufacture of a medicament for treating an inflamed orthopedic joint.

11. Claims 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a benzophenone for the manufacture of a medicament for treating an inflamed orthopedic joint.

12. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a pyrazole ketone for the manufacture of a medicament for treating an inflamed orthopedic joint.

13. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a indole amide for the manufacture of a medicament for treating an inflamed orthopedic joint.

14. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a diamide for the manufacture of a medicament for treating an inflamed orthopedic joint.

15. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a quinazoline for the manufacture of a medicament for treating an inflamed orthopedic joint.

16. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a pyrimido[4,5-d]pyrimidinone for the manufacture of a medicament for treating an inflamed orthopedic joint.

17. Claims 1-4,16,17,30,34-65,80-82 (partially)
Use of an inhibitor of p38 kinase wherein the compound is a pyridylamino-quinazoline for the manufacture of a medicament for treating an inflamed orthopedic joint.

18. Claims 1-4,30,34-65,80-82 (partially) 18
Use of an inhibitor of a 1-aryl-2-pyridinyl heterocycle as specified in claim 18 for the manufacture of a medicament for treating an inflamed orthopedic joint.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem to be solved by the present application is to provide for the treatment of inflamed orthopedic joints.

The proposed solution is to use a compound selected from
i) an inhibitor of a pro-inflammatory interleukin;
ii) an inhibitor of TNF-alpha synthesis;
iii) an inhibitor of membrane-bound TNF-alpha,
iv) an inhibitor of a natural receptor of TNF-alpha,
v) an inhibitor of NO synthase;
vi) an inhibitor of PLA2 enzyme;
vii) an anti-proliferative agent;
viii) an anti-oxidant,
ix) an apoptosis inhibitor selected from the group consisting of EPO mimetic peptides, EPO mimetibodies, IGF-I , IGF-II, and caspase inhibitors,
x) an inhibitor of MMPs,
xi) an inhibitor of p38 kinase, said inhibitor being a
a) diaryl imidizole (sic)
b) N,N'-diaryl urea;
c) N,N-diaryl urea;
d) benzophenone;
e) pyrazole ketone;
f) indole amide;
g) diamides;
h) quinazoline;
1) pyrimido[4,5-d]pyrimidinone
j) pyridylamino-quinazoline.
or
xii) a 1-aryl-2-pyridinyl heterocycle selected from the group consisting of:
a) 4,5 substituted imidazole;
b) 1,4,5 substituted imidizole;
c) 2,4,5 substituted imidizole;
d) 1,2,4,5 substituted imidizole; and
e) non-imidizole 5-membered ring heterocycle.

Said compounds may be administered trans-capsularly, closely adjacent to the outer wall of the capsule or at a location closely adjacent to an outer wall of the capsule. See claims 1, 47, 60.

US5368841 discloses local i.e. intracapsular injection of drugs for treating inflammatory joint conditions. See the passages cited in the search report.

US2001016195 discloses antagonists of IL-1, IL-6, IL-8 to treat osteoarthritis and other forms of arthritis including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis. Said treatment comprises localized administration, including perilesional or intralesional administration of compounds including interleukin 1 receptor antagonist (IL-1 RA) (Amgen) and interleukin 1 receptor type II (IL-1R type II) (Immunex). See the passages cited in the search report.

WO0185179 discloses dextran based composition for injecting into damaged or diseased joints, filling cavities and spaces in artificial joints, applying to joints in connection with post-surgical procedures and injected into joint injury. See the passages cited in the search report.

EP438234 discloses the intrasynovial administration of antithrombin in relation to the treatment of arthritis. See the passages cited in the search report.

US4427649 discloses compsns. useful for treating rheumatoid inflammations of the synovial joints, since they can be injected directly into the cavity of the joint. See the passages cited in the search report.

US6294170 discloses the intracapsular administration of an inhibitor of IL-1, preferably IL-1ra, either alone or in combnation with another drug for treating inflammatory joint diseases. See the passages cited in the search report.

Furthermore, the compounds of the proposed solutions do not share a significant structural element, nor do they belong to a same recognized class of chemical compounds.

According to Article 3(4)(iii) PCT, an international application shall comply with "the

prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

From the above cited documents, it appears that the use of above specified compounds in relation to the treatment of above specified disorders is known in the prior art and can not fulfil the role of special technical feature (general inventive concept) in the sense of Rule 13.2 PCT.

Accordingly there is no new technical effect linking the different groups of inventions.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Consequently the present application lacks unity of invention.

As searching the other inventions would have caused a major additional searching effort, only the first invention was searched.

As the applicant has not had a search report drawn up on the other inventions, this opinion relates only to the invention in respect of which a search report has been carried out, in other words the invention first mentioned in the claims.

Re Item V.

1 The following documents are referred to in this communication:

D1: WO 97/28828 A (AMGEN BOULDER INC; COLLINS, DAVID, S; BEVILACQUA, MICHAEL, P) 14 August 1997 (1997-08-14)

D2: WO 98/24477 A (AMGEN INC; BENDELE, ALISON, M; SENNELLO, REGINA, M) 11 June 1998 (1998-06-11)

D3: US-B1-6 294 170 (BOONE THOMAS C ET AL) 25 September 2001 (2001-09-25)

D4: EP-A-1 133 995 (THE UNIVERSITY OF COLORADO FOUNDATION, INC; AMGEN INC; SYNERGEN, INC) 19 September 2001 (2001-09-19)

D5: GABAY C: "IL-1 TRAP" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 4, no. 5, May 2003 (2003-05), pages 593-597, XP009017868 ISSN: 0967-8298

D6: DAYER J-M: "THE PIVOTAL ROLE OF INTERLEUKIN-1 IN THE CLINICAL MANIFESTATIONS OF RHEUMATOID ARTHRITIS" RHEUMATOLOGY, OXFORD UNIVERSITY PRESS, LONDON, GB, vol. 42, no. SUPPL 2, May 2003 (2003-05), pages II03-II10, XP008041555 ISSN: 1462-0324

D7: US 2001/016195 A1 (TOBINICK EDWARD L) 23 August 2001 (2001-08-23)

D8: US-A-5 368 841 (TRAUNER ET AL) 29 November 1994 (1994-11-29)

D9: WO 01/85179 A (CLEMSON UNIVERSITY) 15 November 2001 (2001-11-15)

D10: EP-A-0 438 234 (KITA, KIYOSHI) 24 July 1991 (1991-07-24)

D11: US-A-4 427 649 (DINGLE ET AL) 24 January 1984 (1984-01-24)

2 CLAIMS 1-11,30,34-75,80-82

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.
Document D1 discloses (see the passages cited in the search report) the intracapsular administration of an inhibitor of IL-1, preferably IL-1ra, either alone or in combination with another drug for treating inflammatory joint diseases.

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.
Document D2 discloses (see the passages cited in the search report) the intracapsular administration of an inhibitor of IL-1, preferably IL-1ra, either alone or in combination with another drug for treating inflammatory joint diseases.

2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.

Document D3 discloses (see the passages cited in the search report) the intracapsular administration of an inhibitor of IL-1, preferably IL-1ra, either alone or in combination with another drug for treating inflammatory joint diseases.

2.4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.
Document D4 discloses (see the passages cited in the search report) the use of Kineret (anakinra; N(sup 2)-L-methionyl- Interleukin 1 receptor antagonist (human isoform x reduced)) in relation to the treatment of inflammatory joint diseases.

2.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.
Document D5 discloses (see the passages cited in the search report) the use of IL-trap in relation to the treatment of rheumatoid arthritis.

2.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.
Document D6 discloses (see the passages cited in the search report) that Kineret (IL-1ra) offers a new therapeutic modality for rheumatoid arthritis, IL-1 can also be antagonized by the decoy receptor IL-1RII.

2.7 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-11,30,34-75,80-82 is not new in the sense of Article 33(2) PCT.
Document D7 discloses (see the passages cited in the search report) that antagonists of IL-1, IL-6, IL-8 are used to treat osteoarthritis and other forms of arthritis including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis. Said treatment comprises localized administration, including perilesional or intralesional administration of compounds including interleukin 1 receptor antagonist (IL-1 RA) (Amgen) and interleukin 1 receptor type II (IL-1R type II) (Immunex).

2.8 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D8-D11 disclose (see the passages cited in the search report) local i.e. intracapsular injection of drugs for treating inflammatory joint conditions.

3 CLAIMS 1-11,30,34-75,80-82

Claims 1-11,30,34-75,80-82 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT). D1-D3, D7-D11 disclose methods of treating an inflamed orthopedic joint comprising the intracapsular adminstration of drugs, i.e. inhibitors of proinflammatory interleukins. Therefore said claims, as far as novel, can not be considered to involve an inventive step.